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Docket No. 47653.2 (1789)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	J.C. Houck, et al.		
Serial Number:	09/190,043	Art Unit:	1631
Filed:	November 10, 1998	Examiner:	M. Borin
For:	SMALL PEPTIDES AND METHODS FOR TREATMENT OF ASTHMA AND INFLAMMATION		

CERTIFICATE OF MAILING

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231 on January 16, 2001.

Deborah Barfield
Deborah Barfield

Honorable Commissioner for Patents
Washington, DC 20231

Sir:

DECLARATION OF JOHN LIPANI, M.D.

I, John Lipani, hereby declare that:

1. I am a citizen of the United States of America and, presently, I am Chairman of the Scientific Advisory Committee of Histatek, LLC, the assignee of the present application.

2. I hold a M.D. degree from Tulane University. I held a Fellowship in Rheumatology at the University of Washington and had a clinical practice as a rheumatologist for about 18 years, during which I conducted clinical research in

connection with a variety of new anti-inflammatory compounds. Prior to my present position at Histatek, I was Vice President, Clinical Development for Abgenix, Inc. andGroup Director of Inflammatory Disease Development for Smith Kline Beecham. Thus, I have been involved in development efforts for numerous compounds in the anti-inflammatory field and have over 27 years experience in research and development in the anti-inflammatory field. A copy of my curriculum vitae is attached hereto as Attachment A.

3. I have read and understand the Office Action of August 14, 2000, including the references cited therein.

4. The present invention is directed to a method for the treatment of an allergic reaction using f-Met-Leu-Phe-Phe.

5. Based on my knowledge and experience in the field, it is my opinion that, prior to the present invention, it was well known to those skilled in the art that formyl methionyl peptides have pro-inflammatory activity.

6. Although it was suggested by Gleisner et al. that f-Met-Leu-Phe inhibited degranulation of mast cells, many publications taught the pro-inflammatory properties of the f-met peptides. Indeed, Kermode et al. taught that f-Met-Leu-Phe-Phe was the most potent inflammatory agent of the f-met peptides.

7. However, surprisingly, the present inventors have discovered that f-Met-Leu-Phe-Phe, can provide a useful anti-allergenic effect by inhibiting the inflammatory response.

8. In the Office Action dated August 14, 2000, the examiner states:

> . . . the essential difference in the effect of a biological mediator (such as F-Met peptide) when it is used alone as compared to its use in the presence of another pro-inflammatory agent. Cellular response to f-Met peptides (which can be described as inflammatory response) is the same type of reaction which mediates response of the organism to a foreign infection. It is well known in the art that biological mediators such as chemotactic factors stimulate the migration of neutrophils from circulation into sites of infection or tissue damage. These mediators are also believed to increase cell adhesion to injured sites and to activate neutrophils to release toxic agents such as oxygen metabolites and proteases. Thus, in the presence of a provoked infection the response caused by f-Met peptides have protective, anti-inflammatory function.

9. It is true that the prior art teaches that:

> Cellular response to f-Met peptides (which can be described as inflammatory response) is the same type of reaction which mediates response of the organism to a foreign infection. It is well known in the art that biological mediators such as chemotactic factors stimulate the migration of neutrophils from circulation into sites of infection or tissue damage. These mediators are also believed to increase cell adhesion to injured sites and to activate neutrophils to release toxic agents such as oxygen metabolites and proteases.

However, those responses are "pro-inflammatory" responses. The claimed composition of the present invention blocks those responses. Thus, the claimed composition has an "anti-inflammatory" response.

10. The examiner concludes:

> Thus, in the presence of a provoked infection the response caused by f-Met peptides have protective, anti-inflammatory function.

This conclusion is erroneous. First, based on my knowledge and experience in the art, there has never been even a hint of a suggestion that a doctor should treat an infection with fMLP. Indeed, such a treatment would aggrevate the pro-inflammatory response already caused by the infection and crate further damage to tissue. Further, characterizing this effect as anti-inflammatory is completely erroneous.

11. The examiner states further that:

> An example of an agent which, similarly to f-met peptides, can be pro- or anti-inflammatory was given in the previous Office action: effects of colony-stimulating factor (CSF) are similar to those of formyl peptides. See, e.g., Beaulieu et al., Wright et al.. CSF is one of theleading mediators of inflammation. See, e.g., al-Janadi et al. At the same time CSF is being used to treat inflammation. See, e.g., Burak et al.

Contrary to the examiner's statement, based on my knowledge and experience in the art, CSFs are not used to treat infection. The CSFs are administered to support patients with overwhelming infection who do not have the white cells to mount a defense. The CSFs stimulate specific lineages of white cells in the bone marrow deficient patient. CSFs are not *pre se* inflammatory mediators as is TNF or Il-1, etc. (Nemunaitis J, Blood, 1991)

12. Based on my knowledge and experience in the art, it is my opinion that no doctor would administer a pharmacological composition to induce a "pro-inflammatory" response.

13. The examiner also states and concludes that:

> Characteristically, . . . the effect of the claimed composition is demonstrated only as inhibitor of inflammatory effect caused by another f-Met peptide, fMLP. The absence . . . of showing of the effect of fMLPP alone is not surprising because Kermode shows (Table 2) that fMLPP (the peptide of the claimed composition) is more potent chemotactic agent and stimulator of neutrophil degranulation than fMLP (the peptide used as "pro-inflammatory" agent). One would expect that fMLPP, alone, would be at least as "pro-inflammatory" as fMLP.

14. However, Kermode conducted *in vitro* tests using rabbit neutrophils that were suspended in solution containing salts, BSA, buffer and for some tests glucose. We have found that such *in vitro* tests are not a predictor of the bioactivity of fMLPP *in vivo*. Although based on the teachings of the prior art, " [o]ne would expect that fMLPP, alone, would be at least as 'pro-inflammatory' as fMLP," as concluded by the examiner, that is an erroneous expectation. Further, based on the teachings of the prior art, one of ordinary skill in the art would not expect fMLPP to act any differently after prior treatment with fMLP.

15. Based on my knowledge and experience in the art, there is not a direct relationship between *in-vitro* observations and *in-vivo* effects. The statements by the examiner based on Kermode ignore the complexities of the *in-vivo* state, such as feedback loops and redundant pathways.

16. HK-X (f-met-leu-phe-phe) is a small peptide that Applicants discovered to have anti-inflammatory effect, and which has been found to be antagonistic to both

the formyl peptide receptor (FPR) and the integrin VLA-6. Although it is related to a family of inflammatory molecules (e.g., f-met-leu-phe), HK-X has been shown to block inflammatory pathways utilizing G-protein signaling and the α-6 moiety of VLA-6.

17. It is my understanding that the Examiner contends that, based on Kermode et al, "one would expect that fMLPP, alone, would be at least as "pro-inflammatory" as fMLP." The experiments conducted by Dr. Clagett show the opposite result, that is, fMLPP is anti-inflammatory and also inhibits the pro-inflammatory effects of fMLP.

18. Based on my knowledge and experience in the field, it is unacceptable to use an inflammation promoting agent (e.g., f-met-leu-phe) as a therapeutic agent.

19. Based on my knowledge and experience in the field, prior to the present discovery by Applicants, no one would have considered the use of f-met-leu-phe-phe to treat an allergic reaction.

20. I have read the Declaration of Dr. Clagett that is being submitted in response to the outstanding Office Action and I agree with the conclusions and opinions expressed by him.

21. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and, further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Codes, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

10/9/01
Date

John Lipani, M.D.